WHAT IS CLAIMED IS:

1. A method for screening for the bioactivity of a candidate compound toward a group of related target proteins in a proteomic mixture of proteins from a cell, employing at least one probe, each probe characterized by comprising a reactive functionality group specific for said group of target proteins and a ligand, each probe of the formula:

R (F – L) -X

wherein:

X is a ligand for binding to a reciprocal receptor and/or providing a detectable signal;

L is an alkylene, oxyalkylene or polyoxyalkylene linking group, wherein said oxyalkylenes are of from 2 to 3 carbon atoms;

F is a phosphonate or sulfonyl functional group reactive at an active site of a target enzyme; and

R is bonded to F and a moiety of less than 1kDal providing specific affinity for said enzymes, and when F is phosponate, F is fluorine and when F is sulfonyl, R is an aryl or heteroaryl group;

said method comprising:

combining at least one probe with an untreated portion of said mixture and with a portion inactivated with a non-covalent agent under conditions for reaction with said target proteins;

sequestering proteins conjugated with said at least one probe from each of said mixtures;

determining the proteins that are sequestered; and

comparing the amount of each of the proteins sequestered from the untreated portion and the inactivated portion as indicative of the bioactivity of said candidate compound with said target proteins.

2. A method according to Claim 1, wherein said probe is a fluorophosphonyl and said enzymes are serine hydrolases.

3. A method according to Claim 1, wherein said probe is a sulfonate, R is a heteroaryl and said enzymes are aldehyde dehydrogenases.

4. A method according to Claim 3, wherein said heteroaryl is pyridyl.

5. A method according to Claim 1, wherein X is biotin.

6. A method according to Claim 1, wherein said non-covalent agent is heat.

7. A method for screening for the bioactivity of a candidate compound toward a group of related target proteins in a proteomic mixture of proteins from a cell, employing at least one probe, each probe characterized by comprising a reactive functionality group specific for said group of target proteins, a ligand and having other than the natural isotope distribution of at least one element, each probe of the formula:

R (F – L) -X

wherein:

X is a ligand for binding to a reciprocal receptor and/or providing a detectable signal;

L is an alkylene, oxyalkylene or polyoxyalkylene linking group, wherein said oxyalkylenes are of from 2 to 3 carbon atoms;

F is a phosphonate or sulfonyl functional group reactive at an active site of a target enzyme; and

R is bonded to F and a moiety of less than 1kDal providing specific affinity for said enzymes, and when F is phosphonate, F is fluorine and when F is sulfonyl, R is an aryl or heteroaryl group;

said method comprising:

combining at least one probe with an untreated portion of said mixture and with a portion inactivated with a non-covalent agent under conditions for reaction with said target proteins;

sequestering proteins conjugated with said at least one probe from each of said mixtures;

determining the proteins that are sequestered and the probe by mass spectrometry; and

comparing the amount of each of the proteins sequestered from the untreated portion and the inactivated portion as indicative of the bioactivity of said candidate compound with said target proteins.

8. A method according to Claim 7, wherein the unnatural isotope is hydrogen, carbon or nitrogen.

9. A method for determining in a proteomic mixture the presence of active target members of a group of related proteins, said related proteins related in having a common functionality for conjugation at an active site, employing a probe comsaid method comprising:

combining said proteomic mixture in wild-type form with a probe comprising a fluorophosphonate or sulfonate reactive functionality specific for said active site when active, under conditions for conjugation of said probe to said target members;

combining said proteomic mixture after non-specific deactivation with said probe under said same conditions;

determining the presence of target members conjugated with said probe in said proteomic mixtures in active and inactive form;

whereby when said target members are conjugated to target members in said proteomic mixture in active form and in less amount in inactive form, the presence of active members is determined.

10. A method according to Claim 9, wherein said probe comprises a detectable lable.

11. A method according to Claim 9, wherein said proteomic mixture is the composition from an intact cell.

12. A method for determining in a plurality of proteomic mixtures the presence of active target members of a group of related proteins in each of said proteomic mixtures, said related proteins related in having a common functionality for conjugation at an active site, said method comprising:

combining each of said proteomic mixtures in wild-type form with a probe comprising a reactive fluorophosphonates or sulfonate functionality specific for said active site when active, under conditions for conjugation of said probe to said target members;

determining the presence of target members conjugated with said probe in said proteomic mixtures;

analyzing for the presence of target members conjugated with said probe using simultaneous individual capillary electrokinetic analysis or capillary HPLC;

whereby when said target members are conjugated to target members in said proteomic mixtures, the presence of active target members is determined.

13. A method for determining in a plurality of proteomic mixtures the presence of active target members of a group of related proteins in each of said proteomic mixtures, said related proteins related in having a common functionality for conjugation at an active site, said method comprising:

combining each of said proteomic mixtures in wild-type form with a probe comprising a fluorophosphonate or sulfonate reactive functionality specific for said active site when active, under conditions for conjugation of said probe to said target members;

determining the presence of target members conjugated with said probe in said proteomic mixtures;

analyzing for the presence of target members conjugated with said probe using simultaneous individual capillary electrokinetic analysis or capillary HPLC;

whereby when said target members are conjugated to target members in said proteomic mixtures, the presence of active target members is determined.

14. A method according to Claim 13 including the additional steps of:

inactivating a portion of said protemic mixture;

combining said inactivated proteomic mixture with said probe under conditions for conjugation;

analyzing for the presence of target members conjugated with said probe in said inactivated proteomic mixture; and

rejecting conjugates from said wild-type proteomic mixture in less amount than the amount of conjugate from said inactivated mixture.

15. A method for determining in a plurality of proteomic mixtures the presence of active target members of a group of related proteins in each of said proteomic mixtures, said related proteins related in having a common functionality for conjugation at an active site, said method comprising:

combining each of said proteomic mixtures in wild-type form with a probe comprising a sulfonate aryl or heteroaryl A method for determining in a plurality of proteomic mixtures the presence of active target members of a group of related proteins in each of said proteomic mixtures, said related proteins related in having a common functionality for conjugation at an active site, said method comprising:

combining each of said proteomic mixtures in wild-type form with a probe comprising a fluorophosphonate or sulfonate reactive functionality specific for said active site when active, under conditions for conjugation of said probe to said target members;

determining the presence of target members conjugated with said probe in said proteomic mixtures;

analyzing for the presence of target members conjugated with said probe using simultaneous individual capillary electrokinetic analysis or capillary HPLC;

whereby when said target members are conjugated to target members in said proteomic mixtures, the presence of active target members is determined.
reactive functionality specific for said active site when active, under conditions for conjugation of said probe to said target members;

determining the presence of target members conjugated with said probe in said proteomic mixtures;

analyzing for the presence of target members conjugated with said probe using simultaneous individual capillary electrokinetic analysis or capillary HPLC;

whereby when said target members are conjugated to target members in said proteomic mixtures, the presence of active target members is determined.